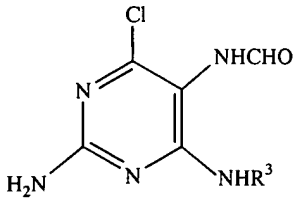
B2 Cont



(VI)

wherein R^3 is [hydrogen or any group which is not attached by a glycosidic bond,] as defined above with a trialkylorthoformate in the presence of an aqueous acid.

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REMARKS

In an Office Action mailed May 11, 1998, claims 9, 18 - 20 are pending and all claims stand rejected. Claim 5 was withdrawn by the Examiner.

Claim 5 has been canceled from the instant application because it is being prosecuted in co-pending application serial number 08/682,743. Claims 9 and 18 - 20 are pending.

The amendment was made in order to clarify the claims as filed.

Claims 9, and 18-20 are rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 5,087,697 (Daluge) in view of U.S. Patent No. 4,916,224 (Vince) or U.S. Patent No. 5,049,671 (Daluge). Applicants respectfully traverse the rejection. The unprotected amino group at the two position of the instant compounds is significant. Two acyl groups, at positions two and five of the pyrimidine ring of '697 compounds further delocalize the amino lone pair groups, serving to activate the 4,6 dichloro substituents of the compounds of formula (VII) of the '697 reference toward displacement by amines. Thus, 4,6,-dichloro pyrimidine compounds disclosed in

the '697 patent are very reactive. Reaction of an amine with these compounds results in mixtures of compounds, with resulting waste of precious amine. The compounds in the mixture are difficult to separate, resulting in low yields, thus precluding large-scale synthesis (specification at page 1; see Example 17 of '697). Reaction of an amine with the 4,6-dichloro pyrimidine compounds wherein the amino group at the two position is not protected (compounds of formula (III) of the instant application) with an amine results in the formation of one product, which is a solid, in high yield, eliminating the need for chromatographic purification (specification at page 13).

Furthermore, deprotection (deacylation) at the 2-position of compounds of formula (II) of the '697 reference is not trivial; the acid or base required causes some hydrolysis of the 6-chloropurine to 6-oxo. An advantage of compounds of formula VI of the instant application over the previously-described N-2-acylated derivatives, is greater ease of synthesis. Furthermore, the purines generated from the compounds of the instant application by the claimed process do not require deprotection.

Use of the 5-formamido intermediates of formula (VI) of the instant application in the synthesis of 9-substituted-2-amino-chloropurines represents a significant improvement over previously published syntheses utilizing triaminopyrimidine intermediates such as compound 6b of the '224 reference or compounds of formula (III) of the '671 reference. Compounds of the '671 reference differ from those of the instant application in that the former compounds lack a chloro group at the 4 position of the pyrimidine ring and a formyl group at the 5 position. The previously-described routes to intermediates such as 6b of the '224 reference are longer, and the number of steps to the purine targets after incorporation of the group R^3 is greater (instant specification at page 13). Triaminopyrimidine intermediates such as 6b are air- and light-sensitive and extremely difficult to purify due to their polarity and metal-chelating abilities (specification at page 13). The 5-formamido intermediates of the instant application are easily and directly attainable from compounds of formula (III) of the instant application (specification

at page 3) in one step and are generally solids which are stable and easily-purified by precipitation from a suitable solvent (specification at page 13).

Therefore, '697, in view of '671, and '224 does not suggest to one of ordinary skill in the art the desirability of modifying the '697 compounds to the instant compounds. Likewise, the references taken together do not motivate or suggest to one of ordinary skill in the art that the instant compounds can be made according to the claimed processes with a reasonable expectation of success. "Obvious to try" is an improper basis for a §103 rejection when there is no suggestion or expressed expectation of success in the prior art that would have led one to perform the experimentation. Therefore, Applicants respectfully submit that the claims are not *prima facie* obvious in view of U.S. 5,087,697; U.S. Patent No. 4,916,224; or U.S. Patent No. 5,049,671. Applicants respectfully request withdrawal of the rejection.

Claim 9 is rejected under 35 U.S.C. §102(b) as being anticipated by EP 413544. The compounds of EP413 544 are outside the scope of the instant application. Please note that the 5-formamido intermediates and ring closure process of the instant specification exclude amines where R^3 is OR or OH, because these amines are unstable under the conditions required for condensation of the amine with the dichlorpyrimidines. Furthermore, the process of EP 413544 is not performed by reacting a compound of formula VII of the reference with alkylorthoformate in aqueous acid. The EP 413544 process results in complex mixtures, decomposition, the necessity for harsh conditions, and low yields (see Example 1 of EP413544). In contrast, the instant process results in pure product in high yields (see, for example, Example 8). Therefore, since compounds of formula (VII) are not encompassed within EP413544, applicants request withdrawal of the rejection under 35 U.S.C. §102(b).

Claims 9, and 18 - 20 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 9, 18, and 20 have been amended to more particularly describe the invention with respect to the definition of R^3 and the process of ring closure, as

requested by the Examiner. Support for the amendments is provided at pages 10 -12 of the specification. In reference to the Examiner's comment regarding the term "glycosidic bond", Applicants wish to point out that the term "glycosidic bond" as defined in the chemical literature refers to 1) the ether linkage between monosaccharide units of a polysaccharide *(Grant & Hackh's Chemical Dictionary*, R. Grant and C. Grant, eds., McGraw-Hill Book Company, New York, 1987, p. 266.; *Biochemistry*, L. Stryer, ed., W.H. Freeman and Company, San Francisco, 1981, pp. 136, 357) and 2) in a nucleoside, the bond between the glycosidic C-1 carbon atom of the pentose and N-1 of the pyrimidine or N-9 or the purine base (Stryer, p. 512).

R^3 has been defined as disclosed on pages 10 – 12 of the specification, and the starting material and final product definitions of R^3 are now aligned. Claims 9 and 18 – 20 have been amended to address the Examiner's points regarding the definition of "group", "heterocycle", "ring closure" and "Ac". Applicants believe that claims 9, and 18 – 20 as amended more particularly point out and distinctly claim the subject matter which applicants regard as the invention. Therefore, Applicants respectfully request withdrawal of the rejection of claims 9 and 18 – 20 under 35 U.S.C. §112.

The amendment to the title more accurately describes the invention.

In view of the amendments and the foregoing discussion, it is respectfully submitted that the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted,

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